amendments and new claims are found in the originally filed specification and in original claims 10, 11 and 13. Various amendments to the specification and drawings also are submitted to correct minor informalities. Again, no new matter is presented by virtue of these amendments.

The drawings were objected to in that they contain figure headings. It is believed that such objection is obviated by the amendments submitted herein. In particular, substitute (informal) drawings are enclosed for Figures 1-3. It is noted that the figure headings have been deleted from such Figures. Additionally, formal drawings for all Figures will be submitted upon Applicant's receipt of a Notice of Allowance in the present application.

Additionally, the specification was objected to on the basis of various informalities. It is believed that the enclosed amendments address these informalities. In particular, multiple occurrences of the term "mamma" have been amended to recite --mammary--. Further, the term "Arachnoidonic" as it appears on page 2, line 21 of the specification has been amended to recite --Arachidonic--. Still further, a section entitled "Brief Description of the Drawings" has been added and the title of the application has been amended as requested in the Office Action.

The Office Action further objects to the specification in that it contains various improper references to trademarks. Applicant respectfully submits that a replacement specification will be submitted under separate cover in which each trademark will be capitalized and be accompanied by the generic terminology wherever appropriate.

Claims 10, 11 and 13 stand rejected under 35 USC §101, on the grounds that a "use" is not patentable.

Applicant respectfully submits that the within amendments obviate the rejection. In particular, claims 10, 11 and 13 have been cancelled, and rewritten as new method claims 14-17.

Reconsideration and withdrawal of the rejection are thus requested.

Claims 10, 11 and 13 stand rejected under 35 USC §112, first paragraph. As the rejection is understood, the position is taken that such claims are allegedly not enabled by the specification.

In particular, the Office Action alleges that no objective evidence is set forth to allow one skilled in the art to predict that the claimed GnRH receptors could be found *in vivo* in tumors of the types of cancer claimed.

Additionally, the Office Action expressly acknowledges that treatment with GnRH analogs is known in the art for hormone-responsive tumors. However, the position is taken that it is not predictable that these methods could be extrapolated to any and all tumors bearing the claimed GnRH receptors.

The Office Action further alleges that there is insufficient guidance to permit predictability of success and thus it would require undue experimentation for one skilled in the art to use the invention as claimed.

The rejection is traversed.

The present application fully satisfies the requirements of 35 USC §112, first paragraph.

For instance, the present application describes Applicant's invention in detail and provides ample enablement to one skilled in the art to make and use the invention. In particular, attention is first directed to page 8, lines 3-24, where the subject matter of the pending claims is discussed and certain advantages over the prior art are noted:

The invention further relates to the use of GnRH agonists or GnRH antagonists to prepare a medicament for the treatment of tumors originating in brain and/or nervous system and/or the meninges. In particular, the invention is directed to the use of GnRH agonists or GnRH antagonists to prepare a medicament for the treatment of Glioblastoma multiforme, medulloblastoma, pinealoma, neuroblastoma, craniopharyngeoma, meningeoma, chordoma, Ewing sarcoma, malignant melanoma, or Kaposi sarcoma. GnRH receptors as well as a GnRH agonist/GnRH antagonist treatment have so far been described neither for craniopharyngeoma nor for meningeoma or chordoma or Ewing sarcoma or malignant melanoma and also not for the Kaposi sarcoma. For these tumors, no blood-brain barrier exists, since they originally are extracerebral, intracranial or peripheral tumors. Therefore, the therapy according to the present invention using GnRH agonists and/or GnRH antagonists or conjugates thereof, respectively, is very advantageous. However, the blood-brain-barrier is permeable for GnRH since a two-direction-system, a bidirectional active transport of GnRH across the blood-brain-barrier exists (Barrera, C., Banks, W.A., Fasold, M.B., and Kastin, A.J., 1991, Effects of Various Reproductive Hormones on the Penetration of LHRH Across the Blood-Brain Barrier, Pharmacology, Biochemistry & Behaviour, vol. 41, 255-257). Thus the treatment by GnRH agonists/GnRH antagonists has advantages over the treatment with tamoxifen for which a blood-brain-barrier exists. For Ewing sarcoma and other peripheral forms of PNET outside of the nervous system, for malignant melanoma and for Kaposi sarcoma, the blood-brain-barrier generally does not play an essential role in the treatment with GnRH agonists/GnRH antagonists since these tumors in most of the cases arise and stay on the outside of the blood-brain-barrier.

Further attention is directed to Table I, as it appears on page 9 of the present application, wherein a list of suitable, preferred GnRH agonists and GnRH antagonists are provided. Other examples of suitable GnRH antagonists are listed on page 9, lines 6-12. References to dosage and administration forms also are provided at pages 9-10 of the present application.

Still further attention is directed to page 11, beginning at line 12, where a detailed example of a preferred treatment protocol is described. The Examples beginning on page 17 provide additional enabling disclosure.

Applicant also notes that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In fact, there are many factors to be considered

when determining whether the specification is enabled and whether any necessary experimentation is "undue". They include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention.

It is respectfully submitted that Applicant's disclosure fully enables the scope of the claims of the application, and that clinical trial data is not required in order to satisfy the requirements of 35 USC §112, first paragraph.

Furthermore, sufficient reasons clearly have not been presented in the Action to establish why one skilled in the art could not make and use the claimed subject matter based on Applicant's disclosure. Such a basis for rejection under Section 112, first paragraph is simply not proper. It is well established that in the absence of any evidence why a supporting disclosure is not sufficient, the mere allegation of inadequacy is not considered to constitute a satisfactory basis for rejection under Section 112, first paragraph. See, for instance, the Manual of Examining Procedure at Section 2164.04 which states (quoting *In re Marzocchi*):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 10, 11 and 13 stand rejected under 35 USC §112, second paragraph. As the rejection is understood, the position is taken that the term "agonist" as it appears in such claims is allegedly indefinite in that it is not defined in the specification.

The rejection is traversed.

The term "agonist" is well known in the art to mean a receptor-specific activator. Similarly, it is well established in the art to which the present invention pertains that the term "antagonist" refers to a receptor-specific blocker. As such, these terms require no supplemental definition in the specification.

As evidence of the terms well-known meanings, Applicant has attached hereto definitions of the two terms "agonist" and "antagonist" as they appear on the web-based medical dictionary "MedicineNet.com". Excerpts of the relevant definitions appear as follows:

> **Agonist**: A drug that binds to a receptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance...
>
> **Antagonist**: In biochemistry, an antagonist acts against and blocks an action... An antagonist is the opposite of an agonist which stimulates an action. Antagonists and agonists are key players in pharmacology and in the chemistry of the human body.

In view thereof, reconsideration and withdrawal of the rejection are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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VERSION MARKED TO SHOW CHANGES

(Additions are underlined and deletions are bracketed.)

IN THE TITLE:

The title as it appears on page 1, lines 1-5 has been amended as follows:

[METHOD FOR RECOGNIZING AND DETERMINING GNRH RECEPTORS AND THE USE OF GNRH AGONISTS AND GNRH ANTAGONISTS AND OTHER GNRH RECEPTOR LIGANDS FOR THE TREATMENT WITH GNRH RECEPTORS OF TUMORS ORIGINATING IN THE BRAIN AND/OR NERVOUS SYSTEM AND/OR MENINGES AND/OR OF KAPOSI SARCOMA]

METHODS FOR TUMOR DIAGNOSIS AND THERAPY USING GNRH AGONISTS AND GNRH ANTAGONISTS

IN THE SPECIFICATION:

At page 1, line 6, the following section and sub-section headings have been inserted:

BACKGROUND OF THE INVENTION.

1. Field of the Invention.

At page 1, between lines 9 and 10, the following section heading has been inserted:

2. Description of Related Art.

The paragraph appearing at page 1, lines 10-14, has been amended as follows:

Post-operative treatment of prostate and [mamma] mammary carcinomas with agonists of gonadotropin releasing hormone (GnRH, in the literature also referred to as luteinizing hormone

releasing hormone; LH-RH) is a standard treatment; cf. Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92; Emons and Schally, 1994, Human Reproduction Update 9, No. 7, 1364-1379.

The paragraph appearing at page 1, lines 15-18, has been amended as follows:

Thus, in various steroid hormone (sexual hormone) dependent malignant tumors, such as [mamma] mammary carcinoma, prostate carcinoma, ovarian carcinoma, and endometrial carcinoma, a double effect has been observed in clinical studies upon treatment with GnRH agonists:

The paragraph appearing at page 1, lines 24-27, has been amended as follows:

The above-mentioned indirect effect due to steroid hormone dependence is known since decades for the prostate and the [mamma] mammary carcinoma; cf. Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92; Jonat et al., 1995, European Journal of Cancer 31A, 137-142.

The sentence appearing at page 1, lines 28-30, has been amended as follows:

The direct anti-proliferative effect of GnRH agonists and GnRH antagonists on e.g. prostate carcinomas, [mamma] mammary carcinomas, and ovarian carcinomas has been confirmed by clinical studies.

The paragraph appearing at page 2, lines 12, to page 3, line 9, has been amended as follows:

Research with cell culture has revealed that GnRH receptors are present on human primary liver cell carcinomas and pancreas adenocarcinomas. In addition, the beginning of a biochemical metabolization with respect to cleavage of GnRH between tyrosine 5 and glycine 6 in rat glioma and rat neuroblastoma has been described; cf. Tao et al., 1991, Neuropeptides 20, 125-131. Ligand binding of GnRH to the GnRH receptor and its signal transduction, however,

take place in a different way, namely at the eighth amino acid of GnRH, arginine, and this exclusively occurs in the case of an intact conformation of the GnRH molecule and its amino acid side chains (Naor, Z., Schacham, Sh., Harris, D., Seger, R., and Riess, N., 1995, Signal Transduction of the Gonadotropin Releasing Hormone (GnRH) Receptor: Cross-Talk of Calcium, Protein Kinase C (PKC), and [Arachnoidonic] Arachidonic Acid. Cellular and Molecular Neurobiology, vol. 15, 527-545). In normal rat adenohypophysis where GnRH receptors reside, GnRH leads to an increased camp production, however, it is still unclear whether this is a direct or an indirect effect (paracrine interaction). For the function of the GnRH receptor in rat including secretion of LH as well as an increased production of LH stimulated by GnRH, the biochemical metabolization of GnRH, e.g. by means of cAMP, plays only an indirect role (Abdilnour, G., and Bourne, G.A., 1995, Adenosine 3'5'-cyclic mono-phosphate and the self-priming effect of gonadotropin-releasing hormone. Molecular and Cellular Endocrinology, 107, 1-7). Naturally, there were found GnRH receptors on human gonadotropin producing pituitary adenomas (Alexander, J.P., and Klibanski, A., Gonadotropin-releasing Hormone Receptor mRNA Expression by Human Pituitary Tumors In Vitro, 1994, Journal of Clinical Investigation, 93, 2332-2339). To treat the indication Pubertas praecox e.g. due to the GnRH-producing hamartoma of the hypothalamus, GnRH agonists were also employed in children in a symptomatic treatment of blocking gonadotropin-producing cells in the adenohypophysis (Mahachoklertwattana, P., Kaplan, S.L., Grumbach, M.M., The Luteinizing-Hormone-Releasing Hormone-Secreting Hypothalamic Hamartoma Is a Congenital Malformation: Natural History, 1993, Journal of Clinical Endocrinology and Metabolism, 77, 118-125).

At page 5, between lines 23 and 24, the following section heading has been inserted:

SUMMARY OF THE INVENTION.

At page 6, following line 2, the following section heading and text have been inserted:

BRIEF DESCRIPTION OF THE DRAWINGS.

Figure 1 shows a plot of Intensity vs. Time for Antide.

Figure 2 shows a plot of Intensity vs. Time for Triptorelin.

Figure 3 shows a plot of Intensity vs. Time for LHRH Hormone.

At page 6, following the newly inserted section entitled "Brief Description of the Drawings", the following section heading has been inserted:

DETAILED DESCRIPTION OF THE INVENTION.

The paragraph appearing at page 10, line 29, to page 11, line 4, has been amended as follows:

The above-mentioned GnRH agonists and GnRH antagonists may be administered in dosages approved for other treatments. There may also be used dosages established during dose finding studies for the use of similar materials (substances, medicaments) such as somatostatin analogues in pituitary adenoma, glioblastoma or pancreas adenocarcinoma, or for phase II studies with GnRH analogues (agonists or antagonists) for other indications, e.g. [mamma] mammary carcinoma, prostate carcinoma or ovarian carcinoma.

The paragraph appearing at page 11, lines 13-22, has been amended as follows:

For the first time, the GnRH receptor concentration in cell membranes of human brain or nervous system tumor cells, i.e. the GnRH receptors on the membrane which are effective in vitro have been determined using a radio receptor assay. With the method according to the invention, the biological activity or specifically the active GnRH receptors, respectively, are determined. For this purpose, radiolabeled [Buserelin®] BUSERELIN, a GnRH agonist, is used as a marker binding specifically to GnRH receptors. Based on radioactive counts of bound [Buserelin®] BUSERELIN the GnRH receptor concentration may be determined. This detection

has already been used for other tumors such as [mamma] mammary carcinoma and the like. The method used according to the present invention measures the GnRH receptor concentration on cell membrane extracts of fresh human tumor tissue.

The paragraph appearing at page 12, line 24, to page 13, line 5, has been amended as follows:

The exact mechanism of action of GnRH agonists or GnRH antagonists on tumors is unknown. For the tumor types known so far having active GnRH receptors such as [mamma] mammary carcinoma, prostate carcinoma and ovarian carcinoma, a locally regulatory autocrine-paracrine system has been proposed in the literature; cf. Irmer et al., 1995, Cancer Research 55, 817-822. For the tumors mentioned, anti-proliferative activities of GnRH agonists or GnRH antagonists have been described in the literature, both in vitro (Palyi et al., 1996, Cancer Detection and Prevention, 20, 146-152; Irmer et al., 1995, Cancer Research, 55, 817-822; Pati et al., 1995, Endocrinology, 136, 75-84) and in vivo or clinically, respectively; cf. Gonzalez-Barcena et al., 1994, The prostate 24, 84-92; Jonat et al., 1995, European J. of Cancer, 31A, 137-142; Emons and Schally, 1994, Human Reproduction Update 9, No. 7, 1364-1379; wherein this anti-proliferative activity goes beyond the anti-proliferative effect to be expected of reversible "chemical castration" by GnRH agonists.

At page 16, line 30, the following section heading has been inserted:

EXAMPLES OF THE INVENTION.

IN THE CLAIMS:

Claims 10, 11 and 13 have been cancelled without prejudice or disclaimer.

The following new claims 14-17 have been added:

14. (new) A method for treating a tumor originating in one or more of the brain, nervous system or meninges of the brain comprising administering to a subject a therapeutically effective amount of a GnRH agonist or GnRH antagonist.

15. (new) A method for treating a Kaposi sarcoma comprising administering to a subject a therapeutically effective amount of a GnRH agonist or GnRH antagonist.

16. (new) A method for treating Glioblastoma multiforme, medulloblastoma, pinealoma, neuroblastoma, craniopharyngeoma, meningeoma, chordoma, Ewing sarcoma, malignant melanoma, or Kaposi sarcoma comprising administering to a subject a therapeutically effective amount of a GnRH agonist or GnRH antagonist.

17. (new) The method according to claim 14, wherein the GnRH agonists or GnRH antagonists are used in combination with a cytotoxic substance.

IN THE DRAWINGS:

Figures 1-3 have been replaced with the attached substitute sheets.

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Agonist: A drug that binds to areceptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance.

An agonist produces an action. It is the opposite of an antagonistwhich acts against and blocks an action.

Agonists and antagonists are key agents in the chemistry of the human body and important players today in pharmacology.

For example, in treating Parkinson disease, the long-used drug levodopa can cause uncontrollable, jerky body movements called dyskinesias that can inhibit a person's ability to functionDopamine agonists mimic the effects of dopamine in the brain by stimulating dopamine receptors with a lower risk of the uncontrollable and irreversible dyskinesias often associated with levodopa therapy.

There are agonists now for many of the known hormones. For example,LHRH (luteinizing hormone-releasing hormone) agonists are similar to LHRH in structure and are able to mimic the effects of LHRH, a hormone that controls sex hormones in both men and women.

The word "agonist" comes from the Late Latin *agnista* contender, from the Greek *agnistes* contestant, from *agn*, contest. An agonist is a chemical contestant or contender.

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Antagonist: In biochemistry, an antagonist acts against and blocks an action. For example, insulin lowers the level of glucose (sugar) in the blood, whereas another hormone called glucagon raises it; therefore, insulin and glucagon are antagonists.

An antagonist is the opposite of an agonist which stimulates an action. Antagonists and agonists are key players in pharmacology and in the chemistry of the human body.

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